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REVIEW ARTICLE

Colon Polyps

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Colon polyps may be single or multiple, noninherited or inherited, histologically may vary from inflammatory, hamartomatous, neurogenic, or adenomatous, and may be benign or malignant. The various recognized syndromes are discussed including their clinical presentation, malignant potential, and associated tumors. Recognition of these clinical syndromes will allow the clinician to categorize the patient and the relative risk. The discussion goes into the genetic studies identifying the adenomatous polyposis coli gene on chromosome 5 q21 and the identification of mutations arising in the DNA repair genes (MSA2, MLH1, PMSI, and M52) in the HNPCC syndrome. This identified two divergent pathologies, both involving ''multiple hits'' with mucosal cells going from normal to adenoma-dysplasia-carcinoma. The understanding of the multiple hit concept with the adenoma-dysplasia-carcinoma progression will aid in the further understanding of the broad neoplastic process.
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KEY WORDS: polyp; hereditary; nonhereditary; dysplasia; microadenoma; aberrant crypt focus; loss of heterozygosity pathway; replication error pathway

INTRODUCTION

The word *polyp* is defined in Dorland's medical dictionary [1], from the Greek *polyposes,* ''a morbid excrescence.'' It now applies to any protrusions from the mucous membrane. With the development of microscopic histology, pathologists and clinicians have equated polyps with adenomatous polyps. But all colonic mucosal smooth or predunculated growths are not adenomatous polyps. As clinicians, we refer to ''colonic polyps'' as any mass of tissue arising from the colonic mucous membrane protruding into the lumen of the bowel. The lesion is then classified histologically including the presence or absence of malignancy.

Further classification of colonic polyps occurs with their number, single, multiple, or diffuse polyposis. In addition, the polyps may arise as part of a hereditary polyposis syndrome or may be sporadic, polyps of a nonfamilial nature.

A clinical classification of the manifestation of colon polyps is given in Table I. They are divided into the nonhereditary and hereditary groups.

NONHEREDITARY POLYPS

Hyperplastic Polyps

These nonhereditary mucosal excrescences are usually small, 5–10 mm in size, and increase in frequency with age. Wattenberg [2] first recognized that hyperplastic polyps have a different cellular proliferation than adenomatous polyps. Histologically, the cells lining the individual crypts are differentiated and mature. Because they are impossible to differentiate grossly from adenomatous polyps, it is imperative that the clinician obtain a biopsy. Some hyperplastic polyps have been found upon biopsy to contain neoplastic adenomatous glands, and they may undergo malignant transformation [3].

Inflammatory Polyps

Nonneoplastic lesions that arise secondary to ulceration and repair and subsequently project above the sur-

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rounding mucosa are termed ''inflammatory polyps.'' They are not a ''pseudopolyp,'' since indeed they present a smooth growth from the mucosal surface. They may be present during an endoscopic procedure and demand a biopsy for histological confirmation. DeDombal et al. [4] report inflammatory polyps occurring in 12.5% of 465 patients with ulcerative colitis. The edematous nodular mucosal islands are seen less frequently in patients with Crohn's disease. The evolution of mature inflammatory polyps composed of mucosa covering a connective tissue core that contains remnants of muscularis mucosa or submucosa has been discussed by Nixon and Mirza [5]. The polyps range in size from 0.2 to 1.5 cm and usually lack the lobulated head seen in the neoplastic adenomas. They can have a thin filiform configuration, or short and broad, bifid or branched, with or without mucosal bridges (Fig. 1A,B). Inflammatory polyps may cause symptoms of bleeding, abdominal pain, and even obstruction, particularly the giant inflammatory polyps and the filiform polyposis that present as a carpet of complex and interconnected fingerlike polyps. These may be mistaken for villous adenomas or carcinomas.

Lymphoid polyps are a variation of inflammatory polyposis. Benign proliferation or hyperplasia of the normally occurring lymphoid tissue of healthy colonic mucosa produces a mass that is a ''polyp.'' Although this hyperplasia or overgrowth is sometimes termed ''benign lymphoma'' or ''pseudolymphoma,'' Nixon and Mirza [5] recommend a reasonable and descriptive term of focal or nodular lymphoid hyperplasia. Enlarged mucosal lymphoid follicles appear endoscopically and radiologically as 1–2 mm polyps. Polypectomy is all that is necessary. The disease process invariably subsides with maturity. Biopsy is extremely important to prevent proctocolectomy for ''polyposis coli.'' The condition is seen in children who present with abdominal pain and hematochezia. The polyps may enlarge in size to 1–2 cm and prolapse through the anus.

The clinically demanding aspect of inflammatory polyposis is the recognition of dysplasia arising in the inflammatory polyps, particularly those associated with ulcerative colitis. It is recognized that colorectal carcinoma arises in 30% of ulcerative colitis patients after 30 years [6]. Morson and Pang [7] identified the clinically useful risk marker of mucosal dysplasia in the ulcerative colitis patients. Colonoscopic surveillance every 1–2 years with multiple mucosal biopsies is now the accepted practice for ulcerative colitis patients with disease of 8–10 years duration. Dysplasia is a neoplastic change in the colonic mucosa that resembles the epithelium of an adenomatous polyp. For the endoscopist, the dysplastic mucosa may be flat and indistinguishable from the surrounding mucosa. Riddell et al. [8] standardized the diagnostic criteria and terminology.

However, a dysplasia-associated lesion or mass may present as a raised nodular plaque with or without multiple small polyps. These lesions may overlie an invasive carcinoma and hence are an indication for colectomy. True adenomatous neoplastic polyps also may arise and must be treated appropriately. The recommendation of surgical colectomy for mucosal dysplasia in ulcerative colitis patients is not straightforward. Many individual factors play a role; however, the goal is cancer prevention and hence early intervention is recommended. Cost effectiveness is used to challenge surveillance and prophylactic colectomy; however, the benefit of prevention justifies the intervention.

TABLE I. Classification of Colonic Polyps

Nonhereditary	Hereditary
Hyperplastic polyps	Hamartomatous polyposis
Inflammatory polyps	Juvenile polyps
Benign lymphoid polyps	Peutz-Jegher's syndrome
Hamartomatous polyps	Ruvelcaba Myhre-Smith syndrome
Canada-Cronkhite syndrome	Devon family syndrome
Sporadic adenoma	Muir-Torre syndrome
	Cowden's disease
	Mucosal neurofibromatosis
	Multiple endocrino neoplasia 2B
	Neoplastic polyps
	Discrete polyps and cancer
	Hereditary nonpolyposis colon cancer syndrome
	Familial polyposis coli
	Gardner's syndrome
	Turcot's syndrome
	Hereditary flat adenoma syndrome

Hamartomatous Polyps

Solitary juvenile polyps cause bleeding in a child. Multiple juvenile polyps are frequently a familial syndrome. Hamartomatous polyps of the entire gastrointestinal tract occur in the Canada-Cronkhite syndrome, an acquired condition with gastrointestinal polyposis associated with ectodermal changes of alopecia, onchodystrophy, and hyperpigmentation. There is no familial history, it has an adult onset, and patients develop a malabsorption syndrome with anemia, weight loss and diarrhea, and electrolyte imbalance to the point of death. Treatment is supportive with vigorous correction of the metabolic defects using blood transfusions and total parenteral nutrition. The judicious administration of antibiotics and corticosteroids may be necessary. The short-term mortality can be as high as 60% and surgery is not the treatment of choice unless malignancy develops [9].

Sporadic Adenomas

The majority (90–95%) of colon cancers arise outside of some recognizable hereditary colorectal syndrome. It is accepted that adenomas precede carcinomas; however, the exact transition is seldom seen. Recently the recog-

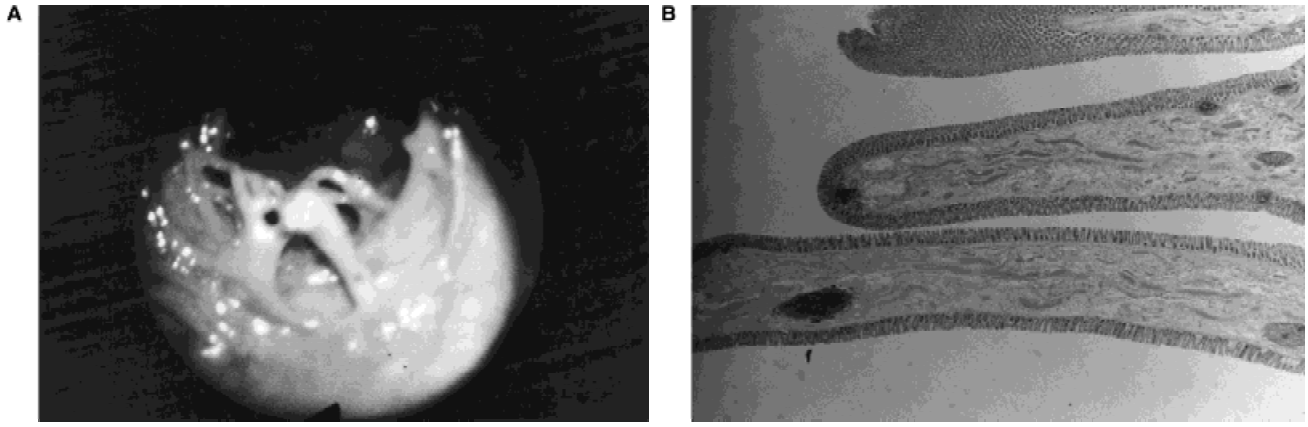

Fig. 1. End-stage inflammatory colon polyps. **A.** Proctoscopic view, 50-year-old male. Note filaform nature and bridging. Courtesy Dr. T. Kanemitsuo, II Surgery Dept., Aichi School of Medicine, Nagoya, Japan. **B.** Histology inflammatory polyps, mature stage. H&E ×10. Courtesy Dr. W. Chang, Dept. Pathology, W.Va. School of Medicine, Morgantown, WV.

nition of the ''aberrant crypt focus'' on the mucosal surface has led to the recognition of microadenomas [10]. Each microadenoma is capable of continued proliferation and development of dysplastic tubules, which when combined form a neoplastic polyp. The adenoma that develops may show a range of dysplastic changes, low grade to high grade, and indeed may already harbor adenocarcinoma [11]. The adenoma-carcinoma sequence remains theoretical and should probably be termed ''dysplasia-carcinoma sequence.'' The etiology of colon neoplastic polyps and associated carcinomas is unknown, but low fiber intake and high dietary fat intake have been implicated. Calcium, vitamin A, C, and E intake and use of NSAIDs have been studied to reduce risk. National clinical trials are underway [12].

HEREDITARY POLYPS

Hamartomatous Polyps

Juvenile polyps of the colon and rectum occur in as many as 1–2% of children [13]. These lesions are hamartomas, usually single. Rectal bleeding is the most common symptom, frequently auto amputation occurs because the stalk lacks the muscularis mucosae. Although most frequent in childhood, they can present in adulthood. Inheritance is believed to be of a Mendelian autosomal dominant type, but a report from St. Marks Polyposis Registry [14] showed one-fourth of the families had more than one affected member, whereas three-fourths did not. Frequently the inherited juvenile polyposes are multiple, from 30 to 300 polyps. Relatives often will demonstrate polyps but will be entirely asymptomatic. Juvenile polyps can exhibit adenomatous dysplasia, and careful biopsy and pathological examination are required. The current treatment recommendation is colon resection of the polyposis segment because bleeding in children can be life-threatening and cancer development in the adult may reach 50% during the lifetime. Colectomy and ileorectal anastomosis are sufficient, the rectal mucosa being readily surveyed and kept free of polyps.

Hamartomatous polyps are present in many other inherited conditions including ''Peutz-Jeghers syndrome,'' an autosomal dominate disorder of intestinal hamartomatous polyps, most commonly found in the small intestine, but it can arise in the stomach, colon, or rectum. The patients show characteristic oral mucosal pigmentation. Symptoms are frequently related to obstruction from intestinal intussusception. Patients with Peutz-Jegher's syndrome have an increased risk of developing cancer and at a relatively young age [15]. Breast, pancreas, and colon cancers are most frequent. A rare ovarian neoplasm, the sex cord tumor with annular tubules can be found in women with Peutz-Jeghers syndrome. In men, an association with sex cord tumors of the testes has been described [16]. Treatment after recognition of the familial syndrome requires removal of symptomatic polyps and careful examination and follow-up for associated cancers.

''Ruvalcaba-Myhre-Smith syndrome'' was described in 1980 [17]. The two patients presented with the triad of macrocephaly, pigmented macules on the penis, and hamartomatous intestinal polyps. As more patients were identified, the syndrome grew to include large birth size, delayed psychomotor development, ocular abnormalities, and a lipid storage myopathy. The hamartomas are seen more commonly in the small intestine, but do occur in the colon. Symptoms usually begin in childhood and consist of pain and bleeding secondary to intussusception. The Riley-Smith syndrome and Bannayan-Lonana syndrome are the same disorder with variation in expression [17].

''Devon Family syndrome'' was described in three women in 1984 [18]. Three successive generations showed recurrent inflammatory polyps, occurring predominantly in the ilium. This type of cluster of patients

with inflammatory fibroid polyps has not been described again, suggesting that the entity is extremely rare.

The ''Muir-Torre syndrome'' arose from reports in 1967 by Muir et al. [19] and in 1968 by Torre [20], who described two patients with benign or malignant sebaceous neoplasms, or less frequently keratoacanthomas, who developed multiple varied adenocarcinomas. The hereditary aspect of Muir-Torre syndrome was apparent by identifying patients with Muir-Torre syndrome as part of kindreds of Lynch syndrome II [21]. Colorectal cancer is the most frequent internal neoplasm and like the Lynch syndrome, occurs in the proximal colon.

''Cowden's disease'' is an uncommon heritable syndrome with enteric polyps. The disease shows involvement of all three dermal layers, the mucocutaneous lesions of facial papules, oral mucosal papillomatosis, acral keratosis, and palmoplantar keratosis along with hamartomas at the gastrointestinal mucosa. The enteric polyps may arise from the esophagus to the rectum and are generally hamartomas but occasionally may be adenomas. Patients with Cowden's disease have an increased risk for a wide variety of cancers. Breast cancer arises frequently as does thyroid cancer [22]. Recognition of the syndrome calls for special attention to the risk of breast or thyroid cancers.

''Mucosal neurofibromatosis'' of the gastrointestinal tract can present upon biopsy as neurofibromas, primarily of nerve sheath origin, ganglioneuromas, and gangliocytic paragangliomas with a major ganglion cell component, or plexosarcomas, which arise from the endogenous enteric plexus. Independently, these lesions present with the clinical symptoms of bleeding or obstruction. This most important presentation is as part of the inherited clinical syndromes. Neurofibromas are the sine quo non of von Recklinghausens' disease, a Mendelian dominant disease of inherited neuro ectodermal dysplasia presenting with cafe au lait spots and neurofibromas arising along peripheral nerve pathways including the gastrointestinal tract. Approximately 25% of these patients will be symptomatic with melena, pain, hematochesia, and obstruction and perforation [23].

The ganglioneuromas are a less common gastrointestinal tumor, and when present are generally part of the multiple endocrine neoplasia type 2B (MEN2B) [24]. MEN1 involves tumors of the parathyroid, anterior pituitary gland, and pancreatic islets. MEN2A involves tumors of the thyroid, parathyroid, and adrenal medulla. MEN2B presents with pheochromocytoma, thyroid carcinoma, and mucosal neuromas. MEN1 and MEN2A are inherited as autosomal dominant diseases, whereas MEN2B may arise as a mutation within an otherwise unaffected family. It is thought to result from a defect in neural crest development. The factor causing neoplasm in these tumors has not been identified. Clinically ganglioneuromatosis of the gastrointestinal tract will approach 100%. The striking feature is the involvement around the oral cavity and eyes, giving a characteristic faces and involvement of the lips and tongue. Although the abdominal pain, vomiting, and diarrhea may be the presenting symptoms, unless diagnosed early and treated, the patients die of hypertension or metastatic medullary thyroid carcinoma.

Neoplastic Polyps

The observation of polyps in the colon probably developed with the practice of cadaver dissection in the seventeenth and eighteenth centuries. The generally accepted first report of numerous colon polyps is by Menzel in 1721 [25]. The advent of the microscope and subsequent histopathology led Woodward in 1891 [26] to divide polyps into ''primary'' with no antecedent disease and ''secondary,'' which followed inflammation and ulceration. In 1882, W. Harrison Cripps presented a paper to the Pathological Society of London establishing familial polyposis of the colon as a clinical entity and noting the familial pattern of the disease and its malignant potential [27]. It remained for Dukes [28] in the 1930s to establish the syndrome of polyposis coli and its autosomal dominant inheritance pattern and the eventual malignant degeneration.

Discrete polyps and cancer. As shown in Figure 2, the polyposis coli syndromes account for 1% or less of colon cancers. Hereditary nonpolyposis colon cancer accounts for 5–6%, leaving 94–95% of colon cancer arising outside these inherited syndromes, often referred to as ''sporadic'' polyps and cancer. The familial relationships of sporadic adenomas and colon cancer was beautifully reviewed by Burt et al. [29]. Utilizing the family histories from the Utah Genealogical Society, the Utah Cancer Registry, and the Utah Death Registry, the authors did pedigree analysis and sigmoidoscopic examination of family members and their spouses. The analysis strongly favored an autosomal dominant inheritance of susceptibility to adenomas and cancer over a recessive inheritance or sporadic occurrence. Their extensive studies show that the observed familial clustering of cancers of the colon occurs on the basis of inherited susceptibility to adenomatous polyps. This underlying susceptibility is important in ~50% of patients with adenomas and cancer of the colon.

Hereditary nonpolyposis colorectal cancer syndrome. The adenoma-carcinoma sequence has given way to the ''aberrant crypt focus'' where these microscopically recognized aberrant crypts turn out to be microadenomas, each a neoplasm with the potential for progressive growth. It is believed that these microadenomas may take 20 years to become a visible adenomatous polyp. The invasive nature is related to the dysplastic changes, high dysplasia harboring invasive adenocarcinoma more frequently than the low-grade dysplasia.

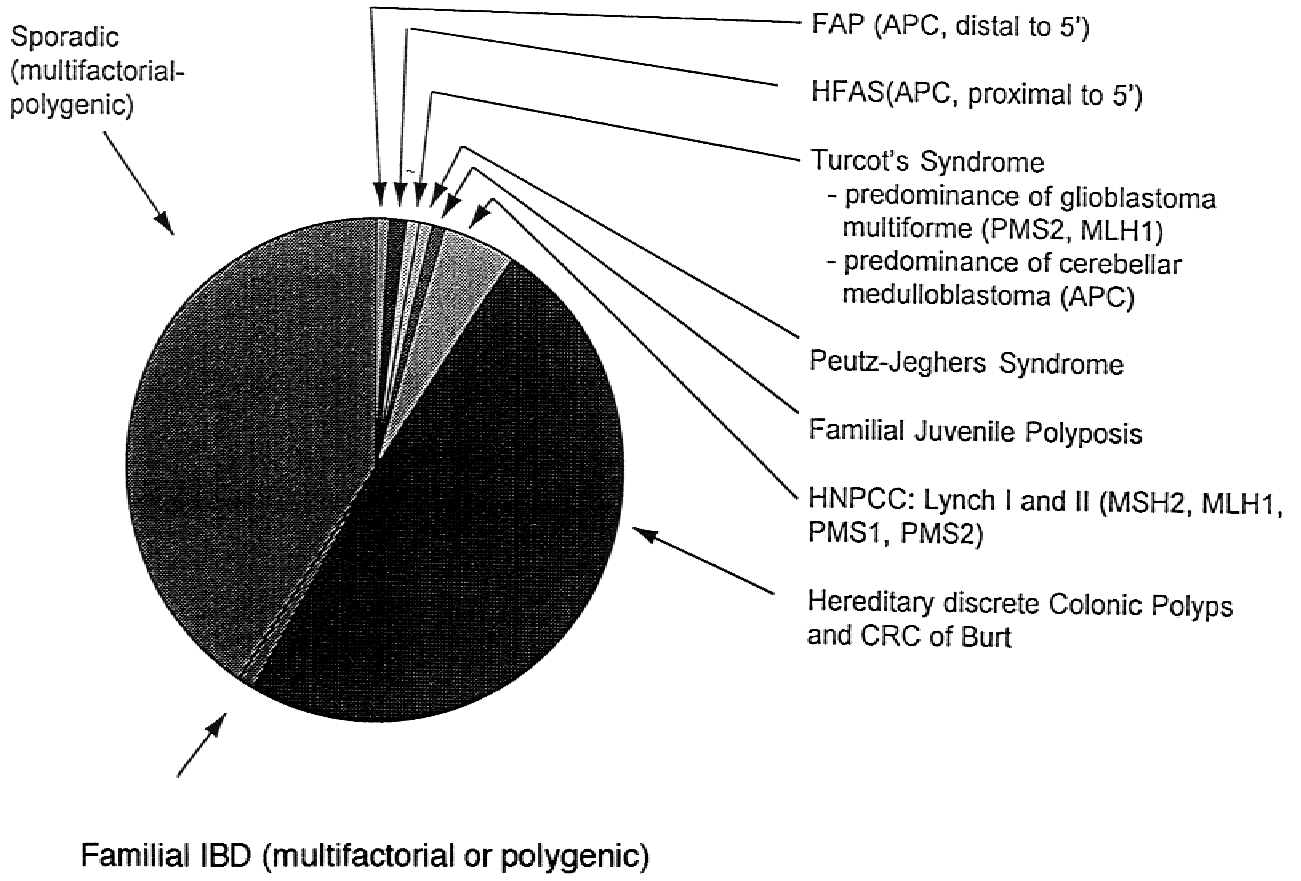

Fig. 2. Pie diagram showing the extant heterogeneity in hereditary colorectal cancer: FAP: familial adenomatous polyposis, APC: adenomatous polyposis coli, HFAS: hereditary flat adenoma syndrome, HNPCC: Hereditary nonpolyposis colon cancer, CRC: colorectal cancer, IBD: inflammatory bowel disease. (Reproduced with permission of the author and publisher, from: Lynch HT, Smyrk T, Jass JR: Hereditary nonpolyposis colorectal cancer and colonic adenomas: Aggressive adenomas? Sem Surg Oncol 1995;11:406–410. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

There is circumstantial evidence for the progression sequence. Knoernschild [30] in 1958 followed 200 patients with adenomatous polyps sigmoidoscopically. After 2 years, one polyp became invasive cancer. Muto et al. [31] described four individuals who declined treatment, and three developed carcinoma in 4–13 years.

The colon polyps in HNPCC are frequently <100, are smaller, and located in the proximal colon. Morphologically they resemble the flat adenoma syndrome. Lynch syndrome I patients have an autosomal dominant inherited colorectal cancer of the proximal colon with an excess of synchronous and metachronous colon cancers. Lynch syndrome II patients have these colonic features plus endometrial carcinoma. Other malignancies in these syndromes include those of the ureter, renal pelvis, stomach, small bowel, ovary, pancreas, biliary tract, skin, larynx, and hematologic malignancy. Lynch syndrome II blends into the Muir-Torre syndrome [21]. The genetic defect is believed to be along the replication error pathway (RER) and involves a mutation in one or more of the DNA repair genes, MSH2 (chromosome 2p) MLH1 (chromosome 3p21), PMSI (chromosome 2q31-33) PMS2 (chromosome 7p22).

Adenomas do occur in HNPCC. The DNA mismatch repair defect in HNPCC may allow accelerated progression of the dysplasia-adenoma-carcinoma sequence. In Lynch's practice, 10 of 53 patients at risk for carcinoma had one or more adenomas [32]. The author recommends genetic counseling and discussions of the problems of DNA testing. If the patient undergoes DNA testing and proves to have one of the HNPCC germline mutations, they recommend colonoscopy by age 20 and repeated annually. It is important to examine the proximal colon. If the patient develops colorectal carcinoma, a subtotal colectomy is indicated because of the risk of synchronous and metachronous colon carcinoma. Because of the increased risk of endometrial or ovarian cancer in women with a documented germline mutation, they recommend a panhysterectomy for women after the child-bearing age.

Familial polyposis coli. Familial polyposis coli was first described as a clinical entity by W. Harrison Cripps

before the Pathological Society of London in 1882 [27]. It remained for Cuthbert Dukes to document the role of hereditary in the syndrome [28], and for Dukes and Lockhart-Mummery to establish the autosomal dominant inheritance pattern [33]. In this disease, the numerous (>100) colonic adenomatous polyps progress to carcinoma by the age of 40. The disease may appear as frequently as 1 in 11,000 births. The absence of a family history may indicate a new mutation, which may have occurred as frequently as in 45% of the patients in the St. Marks Hospital Polyposis Registry.

Gardner's syndrome. The classic description of familial polyposis coli became clouded in the 1950s when Eldon J. Gardner and colleagues published a collection of papers describing a triad of findings, colon polyps, soft tissue tumors, and bony tumors. There followed a flurry of case reports documenting familial polyposis coli with desmoid tumors, fibrosarcoma, thyroid tumors, adrenal, gastric, and pancreatic cancer, and a group of patients with carcinoma of the ampulla of Vater [34].

Turcot's syndrome. This syndrome of familial polyposis coli associated with medulloblastoma and/or chromophobe adenoma was described in 1959 [35]. Phenotypic analysis of pedigrees of patients with familial polyposis coli, Gardner's syndrome, and Turcot's syndrome has shown a shared pleiotrophic gene for familial polyposis coli and Gardner's syndrome, but the expression of Turcot's syndrome required another genetic defect [36]. In 1986, Herrera et al. [37] identified the genetic defect for Gardner's syndrome on chromosome 5q and in 1987 Bodner et al. [38] and Leppert et al. [39] in separate laboratories defined the 5q21 site as the locus for the defect associated with familial polyposis coli. This adenomatous polyposis coli gene fulfills the paradigm of a classic tumor suppressor gene.

Turcot's syndrome remained an enigma. Hamilton et al. [40] studied 15 families including the one originally described by Turcot. They identified two germline genetic defects: (1) a mutation of the APC gene found in familial adenomatous polyposis, and (2) a mutation of a mismatched repair gene that had been identified in hereditary nonpolyposis colorectal cancer. The family members showed other extracolonic lesions including cafe au lait spots, skin cysts, bony tumor, ocular fundus lesions, thyroid adenoma and carcinoma, and uterine carcinoma in addition to the medulloblastoma occurrence. Thus Turcot's syndrome joins familial polyposis coli and Gardner's syndrome with the addition of a mismatched repair gene as seen in the Lynch syndrome.

Hereditary flat adenoma syndrome. This autosomal dominant disorder phenotypically has <100 flat or placque-like colonic adenomatous polyps frequently in the proximal colon. Colon cancer develops in midlife. Adenomas and carcinomas are also observed in the small intestine and gastric fundus. Genetic analysis has revealed linkage to chromosome 5q21-22. This syndrome is considered a variant of familial polyposis coli.

Why the Importance of Colon Polyps

The growth of ''polyps'' on the colonic mucosa is one of the few cancer models we have available in the human. The recognition of various histologic patterns for the polypoid growths has given us insight into their various malignant potential. Inflammatory polyps arising from a ''benign'' disease are now recognized to develop ''dysplasia,'' a recognized precursor to invasive carcinoma. So-called hyperplastic polyps and hamartomas also show some association with dysplasia and malignant degeneration.

It took the autosomal dominant inherited syndromes to attract our attention to the invariable malignant degeneration of these colonic polyps. Studies of histologic type, size, and location all added to our understanding of their malignant potential. It remained, however, for genetic studies really to open the door on the malignant transformation of colonic mucosa to dysplasia to polyp to invasive carcinoma.

In 1988, Vogelstein et al. [41] described the specific loci within the genome that are altered or removed in the progression from a 1 cm adenoma to invasive carcinoma. These steps essentially involved the mutational acceleration of an oncogene associated with the loss of several genes that normally suppress tumorgenesis. This two-mutation step in progression to malignant human cancer was described in detail in a review by Loeb [42]. He proposed that the increase in the mutational rate is due to the abnormal function of genes needed to maintain the integrity of the genome. Lacking an effective repair mechanism, the cells develop a genomic instability that further enhances the accumulation of somatic variations.

From these and other studies, two molecular pathways account for 95% of colorectal carcinoma [43] (Fig. 3). The loss of heterozygosity (LOH) pathway usually begins with a mutation of the APC gene at 5q21 locus. The second pathway, the replication error (RER) pathway, begins with a mutation of one of the genes responsible for DNA repair, so-called mismatch repair genes.

The LOH pathway is shown in Figure 4. The mutation of the APC gene results in the development of a small adenoma. These have a propensity for the left colon. The transition from a small to a significant adenoma is brought about by the activation of the Kirsten-ras (K-ras) oncogene located in chromosome 12. The next step is the generalized deregulation of oncogenes, followed by the sequential inactivation of tumor suppressor genes. These slow or halt all growth, and both must be lost or inactivated for phenotypic expression to occur. For the adenoma to progress a single cell within, the adenoma must lose function of a tumor suppressor gene, usually the DCC gene on chromosome 18q. This yields a clone with

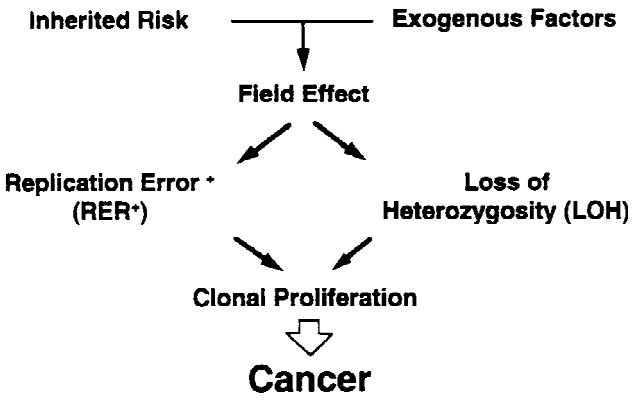

Fig. 3. Pathways to colorectal carcinoma. (Reproduced with permission of the author and publisher from: Allen JI: Molecular biology of colon polyps and colon cancer. Sem Surg Oncol 1995;11:399–405. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

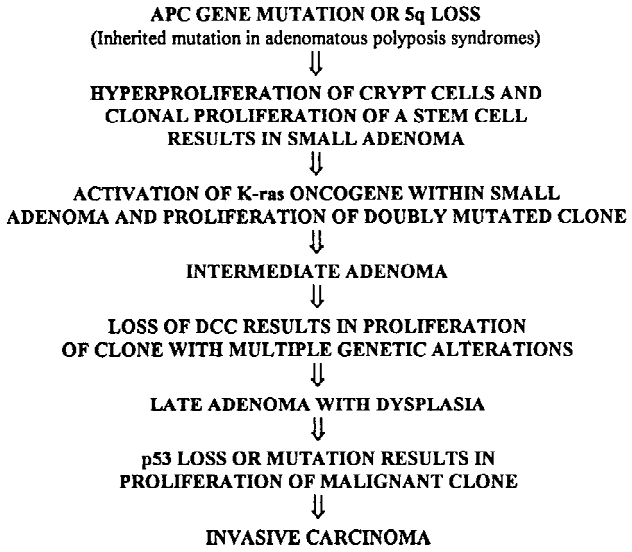

Fig. 4. ''Loss of heterozygocity'' pathway to colorectal carcinoma. (Reproduced with permission of the author and publisher, from: Allen JI: Molecular biology of colon polyps and colon cancer. Sem Surg Oncol 1995;11:399–405. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

multiple genetic alterations, an adenoma with dysplasia. The final hit is the loss or mutation of the p53 tumor suppressor gene on chromosome 17p. The p53 mutations are so frequent and powerful that they induce loss of tumor suppressor activity and produce a gain in oncogenic activity. This may mark the final transition from dysplastic precancer to cancer.

Figure 5 shows the replication error (RER) pathway. Interestingly, this pathway is present in only 20% of distal cancers but in up to 75–80% of proximal cancers such as the HNPCC and flat adenoma syndromes. This pathway is initiated by a somatic mutation in a DNA repair gene (MSA2 chromosome 2p, MLH1 chromosome 3p21, PMS1 chromosome 2q31-33, PMS2 chromosome

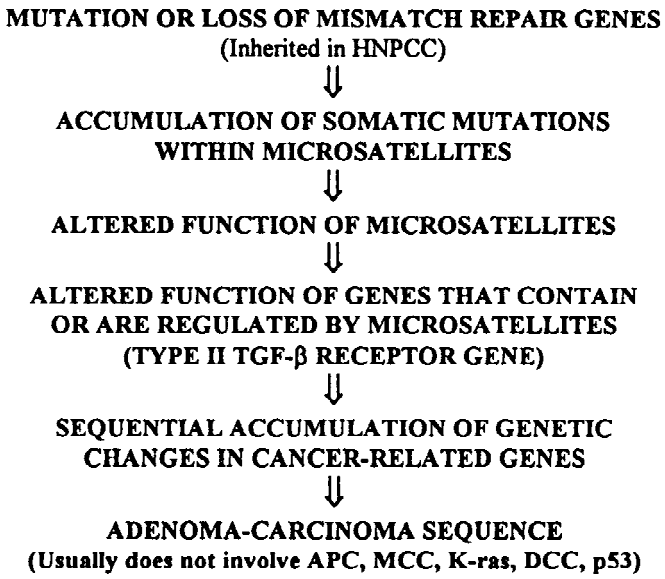

Fig. 5. ''Replication error'' pathway to colorectal carcinoma. (Reproduced with permission of the author and publisher, from: Allen JI: Molecular biology of colon polyps and colon cancer. Sem Surg Oncol 1995;11:399–405. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

7p22). The human genome codes for 60,000 proteins needed daily for a normal cell function. Thus spontaneous damage and increased replication errors lead to an accumulation of somatic mutations. These mutations inactivate a gene that leads to an increase in replication errors in a short segment of the genome that contains microsatellites. As errors accumulate in the microsatellites, malfunction of nearby genes occur. We are just learning the role of this microsatellite malfunction. It does cause malfunction of the gene for Type II transforming growth factor B, a potent tumor suppressor.

This tumor model is providing the laboratory and clinical material for understanding the molecular basis for the dysplasia-carcinoma sequence. This knowledge will not only clarify our approach to colorectal cancers, but may well be applicable to most, if not all, epithelial tumors.

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